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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,597	11/21/2003	Natalie C. Twine	WYE-021	3640

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,597	TWINE ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-17,19 and 20* is/are pending in the application.

4a) Of the above claim(s) *14,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12, 13, and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 11 and 18 have been canceled in the amendment filed on 3/7/2006;

Claims 1 and 16 have been amended as filed on 3/7/2006;

Claims 1-10, 12-17, 19 and 20 are currently pending;

Claims 14, 19 and 20 have been withdrawn;

Claims 1-10, 12, 13, and 15-17 are being examined in this application.

Election/Restrictions

2. Applicants traversed the withdrawal of Claim 14 due to non-elected species as set forth in the previous office action. Applicants request examination of Claim 14 upon determination of the allowability of amended Claim 1. However, Claim 1 is not determined to be allowable at this stage during the prosecution. As indicated in the previous office action: *Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141.*

3. This application contains claims 14, 19 and 20 drawn to an invention nonelected with traverse in the reply filed on 10/7/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

4. This application claims priority to provisional applications 60/427,982 filed on 11/21/2002, and 60/459,782 filed on 04/03/2003. The provisional application 60/427,982 does not provide support for Table 6, which would not obtain the benefit of the priority date (11/21/2002) of the provisional application. (Note: the filing date for the provisional application 60/427,982 was inadvertently cited in the previous office action to be 11/21/2003, which should be 11/21/2002.)

Information Disclosure Statement

5. Applicants have kindly pointed out that page 2 of 2 of the Information Disclosure Statement (IDS) of September 2, 2005 was not considered and initialed by the examiner. An initialed and signed page 2 of 2 of the said IDS (9/2/05) is attached with this office action.

Claim Rejections Withdrawn

6. In light of applicant's amendments to the claims, the following rejections have been withdrawn:

A.) Claims 1, 2, 4-7, 9, 10 and 16-18 are rejected under **35 U.S.C. 102(b)** as being anticipated by Ralph et al (US 6,190,857 B1; 2/20/2001).

B.) Claims 1-6 and 16-18 are rejected under **35 U.S.C. 102(b)** as being anticipated by Olive et al (Immunology and Cell Biology. Vol. 76: 357-362. 1998).

C.) Claims 1-10 and 15-18 are rejected under **35 U.S.C. 103(a)** as being obvious over Ralph et al (US 6,190,857 B1; 2/20/2001), in view of Golub et al (Science. Vol. 286: 531-527; 1999).

Claim Rejections Maintained (103 art rejection)

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 2, 4-7, 9-13 and 16-18 are rejected under 35 U.S.C. **103(a)** as being obvious over Ralph et al (US 6,190,857 B1; 2/20/2001), in view of Liu et al (Infection and Immunity. Vol. 69: 2788-2796; 2001).

The instant claims briefly recite a method comprising comparing gene expression profiles of one or more genes from peripheral blood cell samples (peripheral blood mononuclear cells) between patents with a solid tumor and disease-free humans. If the one or more genes consist of only one gene, then it could not be IL1B, IL6, MMP-9 or FCGR3B. If the one or more genes consist of two genes, then the combination could not be IL1B and IL6. The solid tumor disease could be RCC (renal cell carcinomas), prostate cancer, OR head/neck cancer. The one or more gene is drawn to the TLR2 gene.

Ralph et al teach diagnostic techniques for the detection of human disease states that affect gene expression in peripheral leukocytes as described supra. In addition, the reference also teaches "Genes that were either up regulated or down regulated in blood from metastatic cancer patients were identified. One of the mRNAs identified as being more abundant in the peripheral blood of patients with metastatic prostate cancer was the cytokine interleukin-8 (IL-8). Hence, the immune system is an attractive choice to survey because it would be expected to respond robustly to a malignant disease process. As such, by examining the peripheral blood mononuclear cell population, evidence of cancer presence was obtained without requiring any knowledge of its physical location in the body." (See Paragraph [472] of the reference)

Ralph et al do not specifically teach using TLR2 gene in the method. The reference also does not specifically teach the blood sample is enriched with PBMCs.

However, Liu et al teach TLR2 is predominantly distributed in monocytes/macrophages (would refer to mononuclear cells; See page 2788, left column, 2nd paragraph). The reference also teaches that TLR2 is involved in the signal pathway of NF-κB of the immunosystem. The reference also teaches isolating monocytes (would read on PBMCs) by centrifugation from blood of healthy donors (See Page 2789, right column, 1st paragraph).

Therefore, it would have been prima facie obvious for an ordinary skilled artisan to generate a method comprising comparing gene expression profile of TLR2 gene from peripheral blood samples that is enriched with PBMCs from diseased and healthy humans. Since Ralph et al teach that immune system is an attractive choice to survey because it would be expected to respond robustly to a malignant disease process, and examining the peripheral blood mononuclear cell population would provide evidence of cancer presence without requiring any knowledge of its physical location in the body, a person of ordinary skill in the art would have been motivated at the time of the invention to use compare differential gene expression profiles obtained from peripheral blood samples. Due to the fact that TLR2 is expressed in the PBMCs and is known to be involved in immune signal pathway as taught by Liu et al, an ordinary skilled artisan would motivated to compare TLR2 gene expression profile from samples obtained from diseased and healthy individuals. In addition, the sequence of TLR2 or TIL4 are known in

the prior art as evidenced by the GenBank accession number (AF051152 or SEQ ID No1) recited in Table 4 of the instant specification. The TLR2 RNA transcript would hybridize under stringent condition to CPS No 1 (which consisting of the nucleotides 2325-2635 if SEQ ID No1) of Table 2, and hybridize to a qualifier (e.g. SEQ ID No. 340) recited in Attachment A. Therefore, an ordinary skilled artisan would have reasonable expectation of success of achieving such modifications of comparing gene expression profiles using sequences derived from TLR2 gene.

In conclusion, the invention of the instant claims would have been prima facie obvious over Ralph et al, in view of Liu et al to one of ordinary skill in the art without evidence to the contrary.

Discussion and Answer to Argument (103 art rejection)

9. Applicants traversed over the claim rejections over prior art under 35 U.S.C. 103(a).

10. *Summary of Applicant's Arguments:*

Applicants argue that the cited prior art do not teach motivation to combine the references. Specifically, applicants argue that the cited teaching from the Ralph reference does not amount to a motivation to specifically select TLR2 or any other gene from Table 4 or Table 6.

Applicants also argue the expectation of success was not demonstrated because the Ralph reference identified relatively few genes to be useful, and the Liu reference failed to provide any reasonable basis for concluding that TLR2 would be specifically useful.

11. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record):

(Please note applicant's arguments are in Italic font.)

Applicants argue that the cited prior art do not teach motivation to combine the references.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the combination of the references' (Ralph and Liu) teachings provides motivation to generate a method of comparing the TLR2 gene expression profile from peripheral blood sample of patients and disease-free humans.

Ralph et al teach genes that are either up regulated or down regulated in blood from metastatic cancer patients are identified. One of the mRNAs identified as being more abundant in the peripheral blood of patients with metastatic prostate cancer is the cytokine interleukin-8 (IL-8). Ralph et al teach the immune system is an attractive choice to survey because it would be expected to respond robustly to a malignant disease process. Ralph et al also teach the examination of peripheral blood mononuclear cell population has advantage of providing evidence of cancer presence without requiring any knowledge of its physical location in the body (see para. 472 of the reference). In summary, Ralph et al teach gene expression profile (i.e. genes that are either up or down regulated in blood), and the advantage of monitoring gene expression profile using peripheral blood mononuclear cell population. Therefore, Ralph et al provide strong motivation to study gene expression profile using samples derived from peripheral blood mononuclear cells (PBMCs). Liu et al teach that TLR2 is expressed in PBMCs and involved in the signal pathway of NF-κB of the immunosystem. Because Ralph et al teach

the advantage of studying different gene expression in the immune system using sample derived from PBMCs, one of ordinary skilled in the art would have been motivated to study genes that are know to be expressed in PBMCs, and are also known to be involved in the signal pathway of the immunosystem. In addition, Ralph et al teach methods of detecting cancer in subjects by measuring gene expression levels of genetic markers (see Abstract of the reference). Liu et al teach that TLR2 activates NF-κB (see pg 2788, right col., 1st para), which is known to be involved in tumor signaling pathway, as evidenced by Mayo et al (Biochimica et Biophysica Acta. Vol. 1470: M55-M62; 2000; See Abstract of the reference). Therefore, a person of ordinary skill in the art would have been motivated to use TLR2 as a genetic marker for cancer because of the involvement of TLR2 in the tumor signaling pathway, and to monitor TLR2 gene expression profile using samples derived from PBMCs to monitor cancer progression and/or diagnosis.

Applicants also argue that "Given that Ralph identified relatively few genes to be useful, and Liu failed to provided any reasonable basis for concluding that TLR2 (or any other gene listed in Tables 4 and 6) would be specifically useful, applicants submit that a person of ordinary skill in the art would not have had the requisite expectation that s/he could successfully practice applicants' claimed invention."

Applicant's argument regarding the number of genes identified by Ralph et al is irrelevant to the determination of expectation of success. Ralph et al have demonstrated the success of a method of comparing gene expression profiles in patients and non-patients using samples derived from PBMCs. Liu et al teach that TLR2 gene is known and differentially expressed in PBMCs. In addition, the techniques for monitoring gene expression profiles for various genes are known in the art as demonstrated by Ralph et al and Liu et al. One of ordinary

skill in the art would have reasonable expectation of success to compare gene expression profiles of specific genes (such as TLR2) that are known in the art using known methods and techniques.

New Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

12. Claims 1-10, 12, 13, and 15-17 are rejected under 35 U.S.C. 103(a) as being obvious over Ralph et al (US 6,190,857 B1; 2/20/2001), in view of Golub et al (Science. Vol. 286: 531-527; 1999) and Liu et al (Infection and Immunity. Vol. 69: 2788-2796; 2001). This rejection is necessitated by applicant's amendments to the claims.

The instant claims are drawn to a method, comprising the steps of: providing at least one peripheral blood sample of a human; and comparing an expression profile of one or more genes in said at least one peripheral blood sample to at least one reference expression protile of said one or more genes, wherein each of said one or more genes is differentially expressed in peripheral blood mononuclear cells (PBMCS) of patients having a solid tumor as compared to PBMCS of disease-free humans, and wherein said one or more genes include at least one gene selected from Table 4 or Table 6, provided that if said one or more genes consist of only one gene, said one gene is not selected from the group consisting of IL1B, ILa6, MMP-9 and

FCGR3B, and further provided that if said one or more genes consist of two genes, said two genes are not IL1B and IL6.

(Note: the instant claim numbers are in bold font.)

Ralph et al, throughout the patent, teach diagnostic techniques for the detection of human disease states that affect gene expression in peripheral leukocytes (reads on peripheral blood mononuclear cells of **clms 1, and 16**; See Abstract). The reference teaches a method of detecting prostate cancer in a biological sample (reads on solid tumor disease of **clms 1, 16 and 17**) comprising measuring the levels of IL-8 or IL-10 in combination with at least one prostate disease marker in said sample (See Claim 1 of the reference), which reads on one or more genes in said peripheral blood sample of **clms 1, 7 and 8**. The reference also teaches the method further comprises of comparing the gene levels with corresponding levels obtained from reference populations of normal individuals (See Claim 1), which reads on comparing expression profiles to disease-free humans of **clm 1 and clm 6**. The reference further teaches that the biological sample comprises peripheral human blood (reads on peripheral blood sample of **clms 1, 3 and 4**; See Claim 3 of the reference, for example). In addition, the reference teaches that the cytokine interleukin-8 (IL-8) mRNAs is identified as being more abundant in the peripheral blood of patients with metastatic prostate cancer (See Paragraph 472 of the reference), which reads on (identifying) the one or more genes is differentially expressed in peripheral blood mononuclear cells of **clm 1** and prostate cancer of **clms 2** and **17**. The reference teaches the biological sample could be a whole blood sample (see paragraph 287), which reads on the whole blood sample of **clm 4**. The reference further teaches that the gene expression level is measured by RT-PCR and immunoassay (see Claims 9, 18, 14 and 15, for examples), which reads on the

RT-PCR and immunoassay of **clm 5**. The reference teaches the confirmation of tumor burden of the diseased individuals in relation to gene levels obtained from the peripheral blood samples (refers to expression profile of the one or more genes in peripheral blood samples of patients having said solid tumor of **clm 7** and **clm 9**; See paragraph 469 of the reference). Furthermore, the reference teaches gene levels in patients with Stage D prostate cancer with metastatic tumors (reads on patients having two different tumors of **clm 10**; See Paragraph 287 and Table 10).

Ralph et al do not specifically teach using the specific statistical analysis tool (such as weighted voting algorithm) as recited in **clms 8 and 15**. The reference also does not specifically teach comparing gene expression profile of TLR2 (a gene selected from Table 4 of the instant specification) as recited in **clms 1 and 16**, and its probe binding properties, as recited in **clms 12** and **13**.

However, **Golub et al**, throughout the reference, teach cancer classification based on gene expression by using statistical analysis including weighted voting algorithm (See Abstract and Page 532, right column, first paragraph), which reads on the weighted voting algorithm of **clms 8** and **15**. The reference also teaches the advantages of using these statistical tools to analyzing gene expression profiles such as "class predictors can be constructed for known pathological categories-reflecting a tumor's cell of origin, stage, or grade. Such predictors could provide diagnostic confirmation or clarify unusual cases."

Liu et al, throughout the reference, teach TLR2 is predominantly distributed in monocytes/macrophages (refers to mononuclear cells; See page 2788, left column, 2nd paragraph), which reads on one or more genes (TLR2) from Table 4 or 6 of **clms 1 and 16**. The reference also teaches amplification of TLR2 cDNA using RT-PCR (amplication of the RNA

transcript of TLR2 gene) using probes (see pg2789, right col.), which reads on the RNA transcripts and their inherent binding properties, as recited in **clms 12 and 13.** The reference also teaches that TLR2 is involved in the signal pathway of NF-κB of the immunosystem. The reference also teaches isolating monocytes (reads on PBMCs) by centrifugation from blood of healthy donors (See Page 2789, right column, 1st paragraph).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate a method comprising comparing gene expression profile of one or more genes (specifically TLR2 gene) from peripheral blood samples using known statistical tools to analyze the expression pattern.

Because Golub et al teach classification based on gene expression profile with weighted voting algorithm is useful in cancer diagnosis and offers an advantage for diagnosis of unusual cases, a person of ordinary skill in the art would have been motivated at the time of the invention to use the statistical analysis taught by Golub et al to process gene expression profile data generated by comparing differential gene expression between diseased and normal humans.

Because Ralph et al teach gene expression profile and the advantage of monitoring gene expression profile using peripheral blood mononuclear cell population as discussed supra, one of ordinary skill in the art would have been motivated to study genes that are known to be expressed in PBMCs, and are also known to be involved in the signal pathway of the immunosystem. Because Liu et al teach that TLR2 is expressed in PBMCs and involved in the tumor signal pathway of NF-κB of the immunosystem as discussed supra (see the Discussion and Answer to Argument section above), one of ordinary skilled in the art would have been motivated at the time the invention was made to compare the gene expression profile from

patients and disease-free humans using genes that are know to be expressed in PBMCs, and are also known to be involved in the tumor signal pathway.

Because the statistical methods are known and are successfully used for comparing differential gene expression profile in cancer patients as taught by Golub et al, an ordinary skilled artisan would have reasonable expectation of success of achieving such modifications. Because methods for monitoring gene expression profiles (for various genes) are known in the art as demonstrated by Ralph et al and Liu et al, and the differentially expressed genes (such as TLR2) are known in the art as taught by Liu et al, an ordinary skilled artisan would have reasonable expectation of success of achieving such modifications.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SL
Art Unit 1639
05/15/2005

PETER PARAS, JR.
PRIMARY EXAMINER

SPE1639